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(54) Title: COMBINATION THERAPY FOR TREATING NEURODEGENERATIVE DISEASE

(57) Abstract: The instant invention provides a novel drug combination comprised of an HMG-CoA reductase inhibitor and a selective COX-2 inhibitor, which is useful for treating, preventing, delaying the onset of and/or reducing the risk of developing Alzheimer's disease. One object of the instant invention is to administer the above-described combination therapy to people who do not yet show clinical signs of Alzheimer's disease, but who are at risk of developing Alzheimer's disease. These individuals may already show signs of mild cognitive impairment. Toward this end, the instant invention provides methods for preventing or reducing the risk of developing Alzheimer's by administering the above-described combination therapy to said at risk persons. Such treatment may halt or reduce the rate of further cognitive decline or, in fact, reverse cognitive decline. The present invention also provides for a method of preventing cognitive impairment or dementia, reducing the risk of cognitive decline or impairment or reducing cognitive decline or impairment resulting from stroke, stroke, cerebral ischemia or de-myelinating disorders.

TITLE OF THE INVENTION

COMBINATION THERAPY FOR TREATING NEURODEGENERATIVE DISEASE

FIELD OF THE INVENTION

The instant invention involves a drug combination comprising a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor and a selective inhibitor of cyclooxygenase-2 (COX-2).

BACKGROUND OF THE INVENTION

Recently, in US 5,840,796 the use of selective COX-2 inhibitors was disclosed for the prophylaxis and treatment of neurodegenerative diseases, including mild cognitive impairment and Alzheimer's Disease. Also mentioned are the treatment of stroke, cerebral ischemia and de-myelinating disorders, each of which may result in cognitive decline or dementia. Similarly, WO 95/006490, published March 9, 1995 discloses the use of HMG-CoA reductase inhibitors such as Mevacor and Zocor in delaying the development of and preventing the onset of Alzheimer's Disease.

The list of HMG-CoA reductase inhibitors which may be used with the present invention include but are not limited to the lactonized and dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof of: lovastatin (MEVACOR®, see US Patent No. 4,342,767); simvastatin (ZOCOR®; see US Patent No. 4,444,784); pravastatin, particularly the sodium salt thereof (PRAVACHOL®; see US Patent No. 4,346,227); fluvastatin particularly the sodium salt thereof (LESCOL®; see US Patent No. 5,354,772); atorvastatin, particularly the calcium salt thereof (LIPITOR®; see US Patent No. 5,273,995); cerivastatin, particularly the sodium salt thereof (BAYCOL®, also known as rivastatin; see US Patent No. 5,177,080), nisvastatin also referred to as NK-104 (see PCT international publication number WO 97/23200) and ZD-4522 (see US Patent No. 5,260,440, and Drugs of the Future, 1999, 24(5), pp. 511-513). The structural formulas of several of these statins and additional HMG-CoA reductase inhibitors are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996). HMG-CoA reductase, is an enzyme involved in the rate-limiting step in the biosynthesis of cholesterol.

The present invention provides for a method of preventing Alzheimer's disease, reducing the risk of Alzheimer's disease, delaying the onset of Alzheimer's disease and/or treating Alzheimer's disease by administering to a patient in need of such treatment a combination of an HMB-CoA reductase inhibitor such as lovastatin and simvastatin (including the open-ring dihydroxy acid forms thereof, and salts and esters thereof) and a selective inhibitor of COX-2.

Improved therapies for treating, preventing and reducing the risk of developing Alzheimer's disease are currently being sought for the large number of individuals who are at risk for this disorder. The instant invention addresses this problem by providing a combination therapy comprising an HMG-CoA reductase inhibitor with a selective inhibitor of COX-2. When administered as part of a combination therapy, the selective COX-2 inhibitor together with the HMG-CoA reductase inhibitor provide enhanced treatment options as compared to administration of either the HMG-CoA RI or the selective COX-2 inhibitor administered alone.

The present invention also provides for a method of preventing cognitive impairment or dementia, reducing the risk of cogintive decline or impairment or reducing cognitive decline or impairment resulting from stroke, multi-infarction dementia, cerebral ischemia or de-myelinating disorders.

SUMMARY OF THE INVENTION

The instant invention provides a novel drug combination comprising an HMG-CoA reductase inhibitor and a selective COX-2 inhibitor, which combination is useful for treating, preventing, delaying the onset of and/or reducing the risk of developing Alzheimer's disease.

One object of the instant invention is to administer the above-described combination therapy to people who do not yet show clinical signs of cognitive impairment or Alzheimer's disease, but who are at risk of developing Alzheimer's disease. These individuals may already show signs of mild cognitive impairment or may be at risk of impairment due to either being homozygous or heterozygous of Apolipoprotein E isoform 4. To this end, the instant invention provides methods for preventing or reducing the risk of developing Alzheimer's by administering the above-described combination therapy to said at risk persons. Such treatment may halt or reduce the rate of further cognitive decline or, in fact, reverse cognitive decline.